DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute for Occupational
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John Guiel
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Dear Mr.Guiel:

Introduction

On March 18, 2005, the National Institute for Occupational Safety and Health (NIOSH) received a request from the management of the U.S. Department of the Interior (DOI), Fish and Wildlife Services (FWS) in Hadley, Massachusetts, for a health hazard evaluation (HHE) regarding potential reproductive health effects of exposure to glyphosate, the active ingredient in the herbicides Roundup® and Rodeo®. Some FWS employees were concerned about information contained in a recent publication from the Institute of Science in Society (ISIS), London, England that indicated an urgent need to review the safety of glyphosate. Throughout the spring and summer, some FWS workers routinely apply herbicides on heavily weeded areas managed by the DOI. The requestors cited concern about glyphosate exposure in women of childbearing age who apply these herbicides. Specifically, they requested information on the potential for increased risk of spontaneous abortion, stillbirths, and bearing children with birth defects. The FWS asked NIOSH to review recent studies that have suggested glyphosate may increase the rates of spontaneous abortion. At the time of the request, no FWS employees had reported adverse reproductive health effects. This finding, coupled with numerous scientific publications that have indicated a low potential for exposure as well as the low toxicity of glyphosate, allowed NIOSH investigators to conclude that a large-scale exposure assessment is not necessary. This letter summarizes information supporting that conclusion and includes recommendations for reducing herbicide exposures.

Background

A primary responsibility of the FWS is to preserve and protect wildlife and wildlife habitats across the U.S. The conservation effort involves periodic applications of herbicides to control weeds and undesirable vegetation in wildlife refuges. The application of glyphosate herbicides (Roundup® and Rodeo®) usually involves spraying the chemicals with a low volume backpack-style sprayer while walking through an area. This work is usually performed by a landscape designer or a field biologist. The primary routes of exposure to pesticide applicators are inhalation of the spray mist and contact with skin (dermal). Skin contact can occur via

deposition of the spray mist and via contact with the concentrated product while preparing and transferring the mixture prior to application.

Toxicology of Glyphosate

Glyphosate is a contact, non-selective herbicide of low toxicity. In studies using rats, the Inhalation Lethal Concentration to 50% of the test animals (LC_{50}) was determined to be greater than 12.2 milligrams/liter of air (mg/L). When orally administered, the lethal dose to 50% of the test animals (LD_{50}) was found to be greater than 5600 mg/kilogram (mg/kg) body weight. When applied to the skin, the LD_{50} was greater than 5000 mg/kg body weight. Additionally, glyphosate has not been determined to be a significant inhibitor of cholinesterase (a necessary enzyme for proper nerve conduction).[1] Glyphosate has been found to be slightly irritating to the rabbit eye and nonirritating to rabbit skin.[2] No birth defects were noted when rabbits were exposed to high levels (30 mg/kg/day).[3] Human skin exposure experiments (intact and abraded skin) showed no difference in irritation when glyphosate-exposed volunteers were compared with volunteers who received exposure to either all-purpose household cleaner, dishwashing detergent, or baby shampoo.[4]

A comprehensive review article that examined more than 180 scientific journal publications on the safety of glyphosate concluded that there was no evidence of adverse effects on reproductive parameters, fertility, or endocrine modulation. Additionally, no evidence of tumorigenic or carcinogenic properties were noted as well as no convincing evidence for DNA damage or significant toxicity in short- mid- and long-term exposure studies.[5] Glyphosate, aminomethylphosphonic acid (AMPA, glyphosate's major biodegradation product), and polyethoxylated tallow amine (POEA, the predominant surfactant in glyphosate solutions), were not shown to cause birth defects. The review also found that when ingested, glyphosate and AMPA are not well absorbed, and both are eliminated from the body unchanged. Absorption through the skin is also very low, and neither glyphosate nor AMPA accumulate in the body.[5]

On March 7, 2005, the ISIS, a non-profit organization, issued a press release concerning glyphosate toxicity stating that, "new research findings are raising serious concerns over the safety of the most commonly used herbicide (glyphosate), and should be sending shockwaves through proponents of genetically modified (GM) crops made tolerant to the herbicide, which now account for 75% of all GM crops in the world." The ISIS press release referenced nine publications as evidence for their position; eight from peer-reviewed journals, and a ninth from an ISIS publication concerning genetically modified crops entitled "The Case for a GM-Free Sustainable World."[6]

The eight referenced scientific journal articles included *in vitro* (meaning in an artificial environment, like a test tube), animal, human case-control, historical cohort, and prospective cohort studies. *In vitro* studies of glyphosate and Roundup® exposure effects on sea urchin embryos described delayed hatching and, with high exposures, toxicity that led to death of the embryos. *In vitro* studies using human placental cells found decreased cell viability and death following Roundup exposure.[7,8] Both studies revealed that Roundup (glyphosate plus a surfactant) was more toxic than glyphosate alone. These in vitro studies did not take into

consideration typical human exposure and uptake of the chemical. Absorption of glyphosate through human skin into human plasma is less than 2%, and, with typical use in a work setting, there is minimal inhalation exposure.[9,10]

An animal study found increases in liver function enzymes and deposition of collagen fibers in the livers of rats exposed to glyphosate, concluding that glyphosate is a potential hepatic toxin.[11] In this animal study, glyphosate solution was administered directly to the stomach of rats every 2 days for 75 days. However, this dose and route of exposure would not be seen in humans except in an intentional ingestion.

Epidemiologic studies have examined the relationship of non-Hodgkin's lymphoma to pesticide exposure in men in Sweden, the Midwestern U.S., and Canada.[12,13,14] The Swedish study found an increased risk for developing non-Hodgkin's lymphoma after glyphosate exposure (OR=3.04, 95% CI: 1.08-8.52), but was based on only four exposed cases. The U.S. study found glyphosate-exposed cases to have twice the risk of non-Hodgkin's lymphoma as unexposed cases (OR=2.1, 95% CI: 1.1-4.0), based on 36 exposed cases. The Canadian study did not find a statistically significant increase of non-Hodgkin's lymphoma risk from glyphosate exposure. Conclusions from the results of these case-control studies may have limitations, such as potential misclassification of pesticide use, multiple pesticide exposures leading to inaccurate conclusions about one particular pesticide, and recall bias. The U.S. study, for example, did not include information on the period of exposure (days, weeks, months, years) or the timing of pesticide use in relation to disease onset. A prospective cohort study of U.S. agricultural pesticide applicators did not find an association between glyphosate exposure and cancer incidence, including non-Hodgkin's lymphoma, although there was a suggested association between multiple myeloma and glyphosate exposure (adjusted OR=2.6, 95% CI: 0.7-9.4).[15] Prospective studies have less potential for recall bias and misclassification than case-control studies.

A historical cohort study, a type of prospective study, of farmers in Ontario, Canada, found associations between glyphosate exposure and spontaneous abortions (OR=1.5, 95% CI: 0.8-2.7) and preterm delivery (OR=2.4, 95% CI: 0.9-7.9), but the relationships were not statistically significant.[16]

One study that was not referenced in the press release was also reviewed. An animal study exposing pregnant rats to different oral concentrations of Roundup found a dose-response relationship to fetal skeletal abnormalities. However, the extremely high doses that resulted in abnormalities in the rat offspring would not be used in residential or commercial Roundup® use, but might be seen during intentional ingestion.[17]

A second analysis of the data from the Ontario farmer cohort study found nearly twice the risk of late spontaneous abortion among women with preconception glyphosate-exposed partners (OR=1.7; 95% CI=1.0-2.9). However, when stratified by maternal age, only those women ≥35 years of age had increased risk (OR=3.2; 95% CI: 0.8-23.0), and this finding was not statistically significant.[18] Women <35 years of age had no increased risk of spontaneous abortion with any pesticide exposure during preconception. The same limitations from the initial data analysis

apply to this study, plus some additional ones, including potential confounding from a maternal history of prior spontaneous abortion, and no consideration of the half-lives of individual pesticides. The authors admit that the analyses were designed to generate hypotheses, not test them.

Occupational Exposure Studies

Currently, there are no workplace exposure limits for glyphosate. However, NIOSH has conducted studies of glyphosate exposure under similar application conditions to those used by FWS employees and concluded that the potential for applicator exposure was very low.[19,20] A Finnish study of forest workers occupationally exposed to glyphosate involved exposure monitoring in the work environment.[21] Ten employees, five with and five without glyphosate exposure, were given a medical exam on the first and last day of the study week, including physical examination, blood and urine analyses, electrocardiogram, and spirometry. Each day, personal breathing zone (PBZ) air samples and end-of-shift urine samples were collected and analyzed for glyphosate and AMPA. PBZ air glyphosate concentrations taken throughout the study week were very low [<1.25 micrograms/cubic meter of air ($\mu g/m^3$)] except for two samples with measurable levels of 2.8 $\mu g/m^3$ and 15.7 $\mu g/m^3$ of glyphosate; the limit of detection (LOD) was 0.3 $\mu g/m^3$. All urine glyphosate concentrations were less than 0.1 nanograms/microliter (ng/µL), and AMPA was not detectable. Other than two exposed employees reporting headache, there were no significant differences between the exposed and control groups. This study concluded that occupational exposure to glyphosate in this setting was limited and no significant health effects were evident. The major limitation of this study was the small number of participants and a relatively short study time period (1 week).

In the scientific literature, the only other occupational study of glyphosate exposure is in nursery workers. Fourteen tree nursery workers had glyphosate exposure measured by using gauze patches outside their clothing (to estimate deposition of glyphosate), hand washes, and urine sampling over a 12-week period. Gauze patches and hand washes contained measurable amounts of glyphosate; urine analyses were all negative for glyphosate, indicating poor absorption.[22]

Summary

A recent report has questioned the safety of glyphosate; however, many of the studies used to support its conclusion had borderline or statistically insignificant findings, had methodologic problems, or used glyphosate exposures much higher than typical human glyphosate exposure. The occupational exposure studies reviewed indicated that exposures are low during mixing and application. While it is difficult to be absolutely certain of its safety profile, Roundup® and other products containing glyphosate and POEA appear safe if used and applied according to manufacturer's recommendations. Nonetheless, it is prudent to minimize the use of herbicides and adopt other measures to reduce employee exposure.

Recommendations

1. Avoid pesticides and herbicides if usage is not essential. Consult County or State agricultural agents to see if there are equally effective organic methods.

2. Add a water-based, non-toxic dye to the herbicide spray mix so applicators can visually identify areas already sprayed. This will help the applicator avoid contact with treated foliage and reduce unnecessary exposure.

3. Use administrative controls such as rotating workers who spray the herbicide to decrease exposure if management and employees are concerned about exposure.

4. Use the appropriate personal protective equipment (PPE), identified on the manufacturers' Material Safety Data Sheet (MSDS), when spraying or mixing herbicides. Examples of appropriate PPE for glyphosate are: disposable or washable coveralls, rubber boots, gloves, and goggles.

This letter closes our file on this health hazard evaluation request. NIOSH recommends that employers post a copy of this letter for 30 days at or near work areas of affected employees.

If you have any questions, please do not hesitate to contact me at (513) 841-4325.

Sincerely yours,

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